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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,506	12/13/2004	Moritz Rossner	085449-0150	6374

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,506	ROSSNER ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-122* is/are pending in the application.

4a) Of the above claim(s) *61-85 and 89-122* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 September 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0904*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Invention II, Claims 86-88, in their response of January 19, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 61-122 are pending. Claims 61-85 and 89-122 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 86-88 are hereby examined.

Priority

The priority date granted for the instant invention is March 13, 2003, the filing date of PCT/EP03/02611, which discloses the elected invention. If Applicants wish to perfect their claim to the benefit of priority to Germany 102 11 063.8, filed March 13, 2002, an English-language translation should be filed.

Drawings-Objections

Figures 24 and 25 are objected to for disclosing sequences that are not identified by a sequence identifier number (SEQ ID NO:). The sequence rules embrace all nucleotide sequences with ten or more bases and all amino acid sequences with four or more amino acids. Said sequences must be disclosed in a sequence listing and identified by a specific SEQ ID NO: (MPEP 2421.02). 37 CFR 1.821(d) requires the use of the assigned sequence identifier number in all instances where the description or claims of a patent application discuss sequences, regardless of whether a given sequence is also embedded in the text of the description or claims

of an application. Applicant is required to check the drawings completely and to make corrections to identify all of the sequences disclosed therein by sequence identifier numbers.

Figures 4, 5, 7, and 8 are objected to for being of such poor quality that the images are not perceivable.

Abstract- Objections

The abstract is objected to.

MPEP 608.01(b) states

> The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Specification-Objections

The first paragraph of the specification should be updated to recite the benefit of priority documents.

The specification is objected to for disclosing sequences that are not identified by a sequence identifier number (SEQ ID NO:). The sequence rules embrace all nucleotide sequences with ten or more bases and all amino acid sequences with four or more amino acids. Said sequences must be disclosed in a sequence listing and identified by a specific SEQ ID NO: (MPEP 2421.02). 37 CFR 1.821(d) requires the use of the assigned sequence identifier number in all instances where the description or claims of a patent application discuss sequences, regardless of whether a given sequence is also embedded in the text of the description or claims

of an application. Applicant is required to check the specification completely and to make corrections to identify all of the sequences disclosed therein by sequence identifier numbers.

Claims-Objections

The claim set is objected to for not beginning with a sentence of which the claims are an object e.g., "We claim" or "The claims are".

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 86-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons. The formatting of Claim 86 renders Claims 86-88 confusing. The formatting "u)" on line 3 indicates that there is a list comprising, at least, "a)-t)". Such a list is not presented in the elected claims and, therefore the skilled artisan would not be apprised on the meaning of "u)" and/or any other missing elements.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 86-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable the skilled artisan to make and use the full scope of the recited invention.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 86-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting protein interaction in a cell using a first fusion protein comprising residues 1-70 of TEV, a second fusion protein comprising residues 71-243 of TEV protease, and a Cre/EGFP reporter, does not reasonably provide enablement for a method of detecting protein interaction in a cell using a first and second fusion protein comprising domains of any protease and any reporter.

Claims 86-88 are so broad as to encompass a functional complementation system for detecting protein interaction comprising a pair of fusion proteins. Each fusion protein of the pair comprises a heterologous peptide fragment and a domain of a protease, wherein each of the two protease domains is inactive by itself while the pair will reconstitute protease activity when brought into close proximity to each other by binding of the heterologous peptide domains of the fusion protein pair. Moreover, the method requires that reconstitution of activity will not occur

when the two protease domains are merely mixed together. The recited method also encompasses the use of any reporter system. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of fusion protein pairs broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. Furthermore the claims require that the fusion proteins have the necessary functional properties of reconstituting an active protease when brought into close proximity to each other by binding of the heterologous peptide domains of the fusion protein pair but not reconstituting an active protease when merely mixed together. In addition reconstitution of the protease activity must activate or inactivate a reporter system. These functional properties are highly dependent on the structure of the individual fragments and will not be present in most fragments of any proteases. It should be noted that there are a large number of proteases each of which have a unique structural and functional domains. As such the structure and function of the described TEV protease domain pairs will not be representative of the structure and function of all fragments of any protease. Thus, in this case the disclosure is limited to systems including fusion proteins comprising only domains of TEV protease and the Cre/EGFP reporter.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims,

and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable (Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a functional complementation system comprising a pair of fusion proteins, and plasmids encoding said fusion proteins, wherein each fusion protein of the pair comprises a heterologous peptide and a domain of any protease wherein each of the two domains are enzymatically inactive while the pair will reconstitute protease activity when brought into close proximity to each other by binding of the heterologous peptide domains of the fusion protein pair. The method also requires that protease activity will not be reconstituted when the fusion proteins are merely mixed together. The specification does support the broad scope Claims 86-88 because the specification does **not** establish: (A) fragments of the sequence of any protease which have the necessary functional properties; (B) guidance for predicting which fragments of the large number of proteases will have the desired characteristics; (C) which reporter systems can be used for the recited method; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a functional complementation system comprising a pair of fusion proteins, and plasmids encoding said fusion proteins, wherein each fusion protein of the pair

comprises a heterologous peptide domain and a fragment of any protease wherein each of the two fragments is inactive by itself while the pair will reconstitute an active protease when brought into close proximity to each other by binding of the heterologous peptide domains of the fusion protein pair but activity will not be reconstituted when the protease fragments are merely mixed together. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of fusion protein pairs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 86-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of methods for detecting protein interaction in a cell using a first and second fusion protein comprising domains of any protease and any reporter. The specification teaches only a single representative species of such methods, using TEV protease. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of methods for detecting protein interaction in a cell using a first and second fusion protein comprising domains of any protease and any reporter. Given this lack of description of representative species encompassed by the

genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al, 2000 in view of Ghelis et al, 1978 and further in view of Carmel et al, 1973. Michnick et al provide a review of methods for detecting protein/protein interaction using complementation strategies. Said methods include expressing a first fusion protein comprising a first interaction partner and part of an enzyme and a second fusion protein comprising a second interaction partner and another part of the enzyme. Intracellular binding of the first and second interaction partners reconstitutes enzyme activity resulting in activation/inactivation of a reporter (Fig 1). The reporter can be assayed by measuring, for example, a colorimetric or fluorometric signal or survival of the cells. Michnick et al do not teach a method wherein the enzyme is a protease. Ghelis et al teach that the two β-barrel domains of elastase can be independently folded and mixed together to generate 2% of the activity (pg 33, parg 2). It would have been obvious to a person of ordinary skill in the art to adapt the method of Michnick et al to use a first interaction partner linked to one domain of elastase and a second interaction partner linked to the second domain of elastase, wherein the reporter comprises a cleavage site for elastase and, when

cleaved, gives a measurable signal. Motivation to do so derives from the desire to detect binding partners. The expectation of success is high, as cellular methods for detecting binding partners using two co-expressed fusion proteins are well-known in the art. Furthermore, methods for detecting protease activity using a reporter are also well known in the art (Carmel et al, 1973). Moreover, since mere mixing of the two domains of elastase regenerates only 2% of the activity, binding of the two fusion proteins would be expected to raise the elastase activity above this low level. Therefore, Claims 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al, 2000 in view of Ghelis et al, 1978 and further in view of Carmel et al, 1973.

Claims 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al, 2000 in view of Bazan et al, 1988 and further in view of Carmel et al, 1973 as evidenced by Stevens, 2000 and Sawyer et al, 1978. The teachings of Michnick et al and Carmel et al are described above. Neither Michnick et al nor Carmel et al, or the combination thereof, teach adapting the method of Michnick et al to use domains of the TEV protease to detect protein/protein interaction. Bazan et al teach that, like elastase, the structure of TEV protease has twin β-barrel trypsin-like folds (pg 7875, parg 2; Fig 3). It would have been obvious to a person of ordinary skill in the art to adapt the method of Michnick et al to use a first interaction partner linked to one domain of TEV protease and a second interaction partner linked to the second domain of TEV protease, wherein the reporter comprises a cleavage site for TEV protease and, when cleaved, gives a measurable signal. Motivation to do so derives from the desire to detect binding partners and the fact that TEV protease has very high substrate specificity (Stevens, 2000). The expectation of success is high, as cellular methods for detecting binding partners using two co-expressed fusion proteins are well-known in the art. Furthermore,

methods for detecting protease activity using a reporter are also well known in the art (Carmel et al, 1973). Moreover, as taught by Bazan et al, like elastase, the three-dimensional structure of TEV protease comprises the twin β-barrel trypsin-like folds, while Sawyer et al teach that chymotrypsin, and other trypsin-family proteases, has a structure very similar to elastase (pg 170-187). Based on the teachings of Bazan et al and Sawyer et al, the skilled artisan would have a high expectation that the complementation method rendered obvious by the combination of Michnick et al, Ghelis et al, and Carmel et al, as described above, could be successfully adapted to use the two domains of TEV protease. Therefore, Claims 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al, 2000 in view of Bazen et al, 1988 and further in view of Carmel et al, 1973, as evidenced by Stevens, 2000 and Sawyer et al, 1978.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
Art Unit 1652